

Recombinant DNA Advisory Committee and Genetic Modification Clinical Research Information System

**Jacqueline Corrigan-Curay, J.D., M.D.
Office of Biotechnology Activities
Office of Science Policy
April 12, 2013**



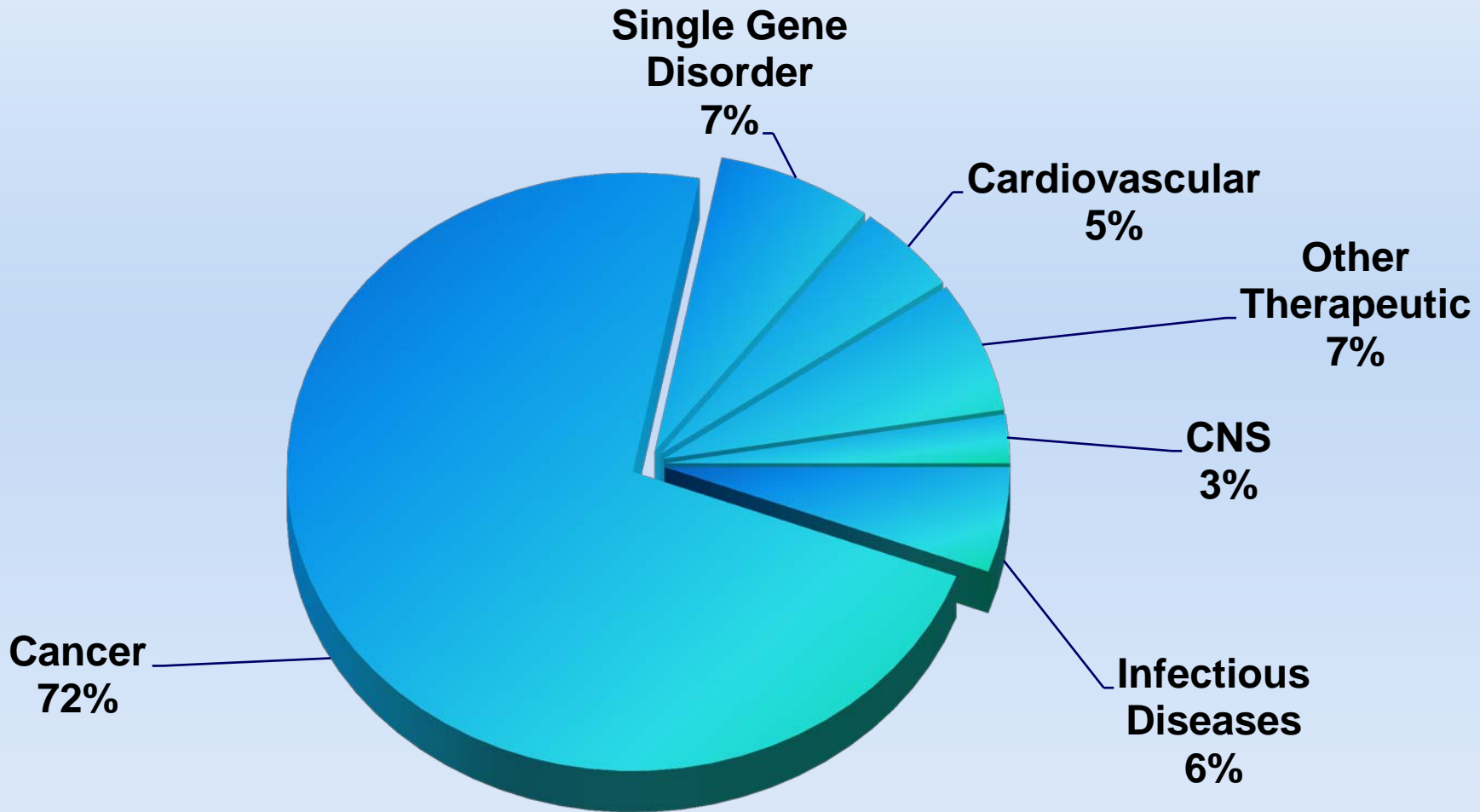


OVERVIEW

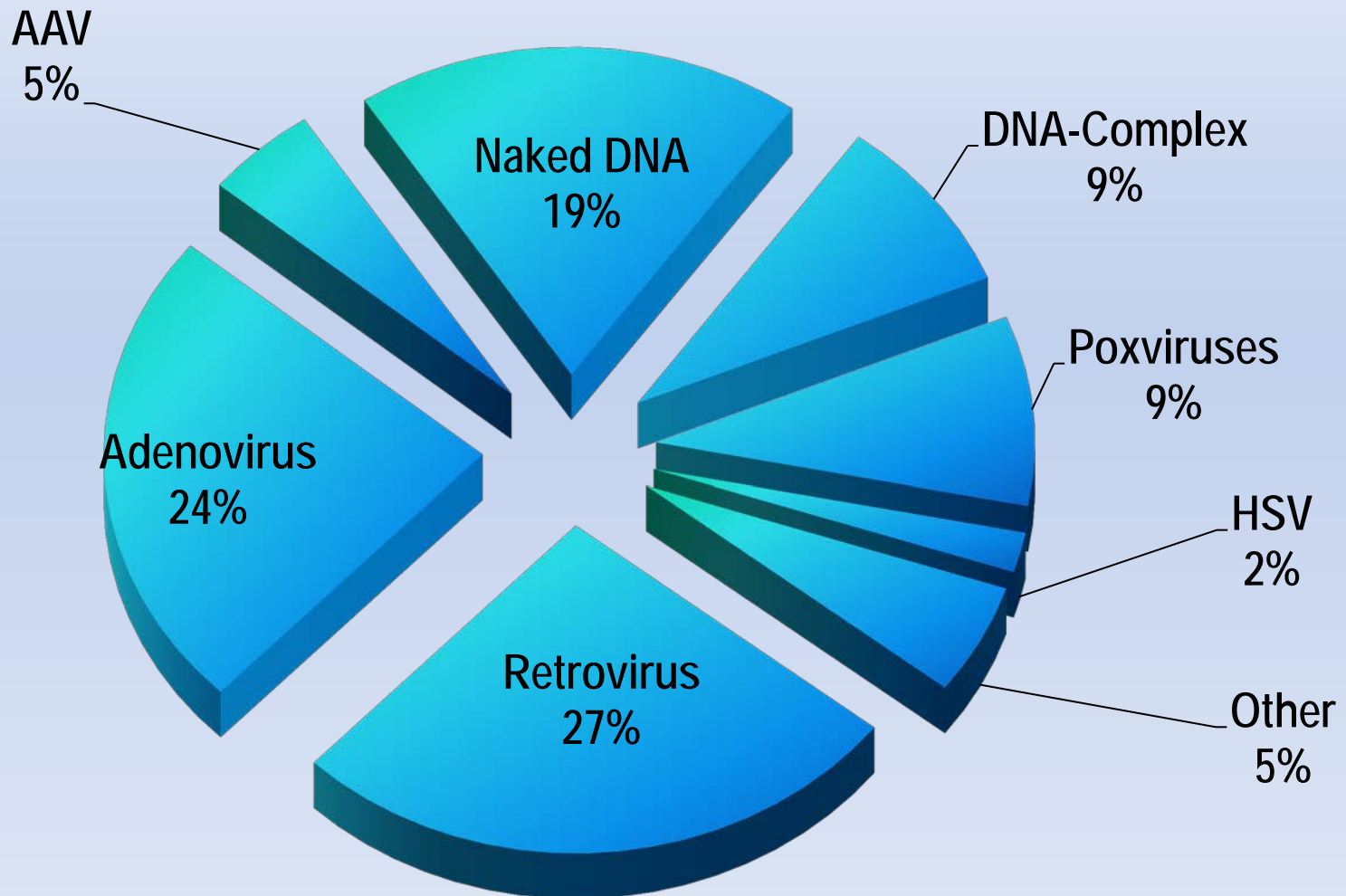
- » **Clinical Gene Therapy: Applications and Vectors**
- » **Role of the RAC and Resources**
- » **The Genetic Modification Clinical Research Information System (GeMCRIS)**

Gene Transfer Trials By Application

2008-2012



Gene Transfer Trials By Delivery System 2005-2012





Recombinant DNA Advisory Committee (RAC)

- **Federal scientific advisory committee with broad clinical and scientific expertise as well as bioethics and public representation**
- **Meets quarterly in open forum with significant webcast audience**
 - **Promotes scientific rigor and ethical conduct of human gene transfer**
 - **Key component of biosafety oversight framework for recombinant and synthetic nucleic acid research conducted in the U.S.**



Clinical Protocol Review Activities

- **A small number of novel clinical human gene transfer protocols reviewed at public meetings**
 - ❑ **Enhances the scientific merit of the protocol**
 - ❑ **Increases the safety for subjects, and as necessary, biosafety protections for researchers, health care workers, close contacts of research subjects**
 - ❑ **Informs the field of new developments**
 - ❑ **Promotes transparency**



Resources from Individual Protocol Reviews

- **Was a Protocol reviewed?**
 - **GeMCRIS**
 - **Protocol List on OBA website**
- **Meeting materials**
 - **Webcast**
 - **Presentations**
 - **Minutes contain final RAC recommendations**
 - **Summaries of selected, related, serious adverse events reviewed by the Gene Transfer Safety Assessment Review Board (GTSAB)**

<http://oba.od.nih.gov/rdna/rdna.html>



Aggregation of Data from Protocols

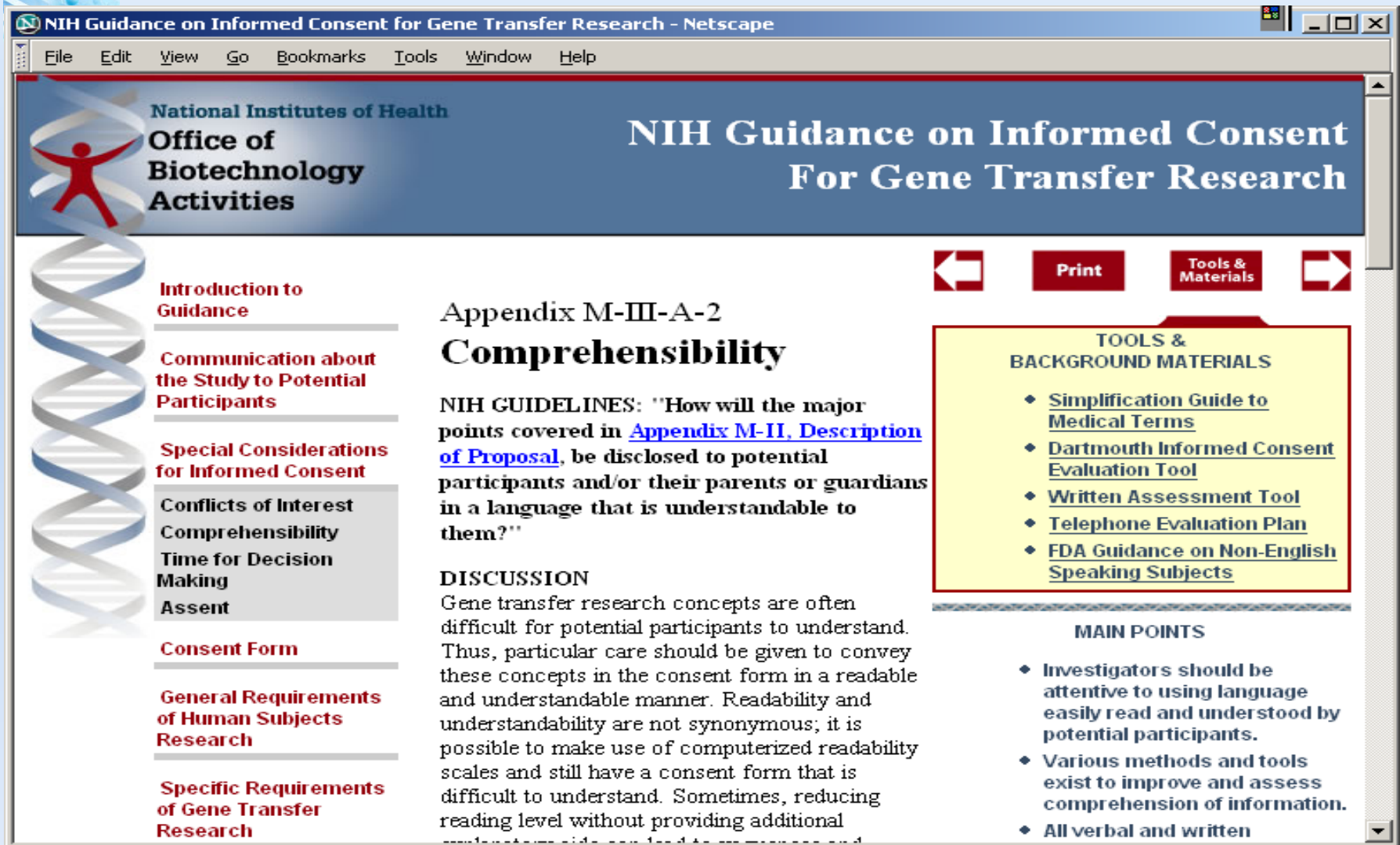
- **Ongoing identification and dissemination of key issues of importance to the field**
 - **Analyses of safety data:**
 - **Becomes the basis of safety symposia examining specific products/trial designs**
 - **Assures the public that potential safety issues are being proactively addressed**
 - **Identification of trends in protocol design, applications, and vectors to allow development of gene therapy workshops**



Recent Workshops

- **Gene Transfer and Rare Diseases (Sept. 2012)**
- **RNA Oligonucleotides: Emerging Clinical Applications (Dec. 2011)**
- **NIH RAC and CliniGene Scientific Symposium on Retroviral and Lentiviral Vectors for Long-term Gene Correction: Clinical Challenges in Vector and Trial Design (Dec. 2010)**
- **Sham Neurological Procedures in Clinical Trials for Neurodegenerative Diseases: Scientific and Ethical Considerations (June 2010)**
- **Gene-Modified T Cells: Challenges in Clinical Trial Design (June 2010)**

Informed Consent Guidance



The screenshot shows a Netscape browser window displaying the NIH website. The browser's title bar reads "NIH Guidance on Informed Consent for Gene Transfer Research - Netscape". The address bar is empty. The menu bar includes "File", "Edit", "View", "Go", "Bookmarks", "Tools", "Window", and "Help". The website header features the NIH logo on the left and the title "NIH Guidance on Informed Consent For Gene Transfer Research" in large white text on a blue background. Below the header, there is a navigation bar with buttons for "Introduction to Guidance", "Communication about the Study to Potential Participants", "Special Considerations for Informed Consent", "Conflicts of Interest", "Comprehensibility", "Time for Decision Making", "Assent", "Consent Form", "General Requirements of Human Subjects Research", and "Specific Requirements of Gene Transfer Research". The main content area is titled "Appendix M-III-A-2 Comprehensibility" and contains the text: "NIH GUIDELINES: 'How will the major points covered in [Appendix M-II, Description of Proposal](#), be disclosed to potential participants and/or their parents or guardians in a language that is understandable to them?'" and a "DISCUSSION" section. To the right of the main content, there is a box titled "TOOLS & BACKGROUND MATERIALS" containing a list of links: "Simplification Guide to Medical Terms", "Dartmouth Informed Consent Evaluation Tool", "Written Assessment Tool", "Telephone Evaluation Plan", and "FDA Guidance on Non-English Speaking Subjects". Below this box, there is a section titled "MAIN POINTS" containing a list of bullet points: "Investigators should be attentive to using language easily read and understood by potential participants.", "Various methods and tools exist to improve and assess comprehension of information.", and "All verbal and written".

NIH Guidance on Informed Consent for Gene Transfer Research - Netscape

File Edit View Go Bookmarks Tools Window Help

National Institutes of Health
Office of
Biotechnology
Activities

NIH Guidance on Informed Consent
For Gene Transfer Research

Introduction to Guidance

Communication about the Study to Potential Participants

Special Considerations for Informed Consent

Conflicts of Interest

Comprehensibility

Time for Decision Making

Assent

Consent Form

General Requirements of Human Subjects Research

Specific Requirements of Gene Transfer Research

Appendix M-III-A-2
Comprehensibility

NIH GUIDELINES: "How will the major points covered in [Appendix M-II, Description of Proposal](#), be disclosed to potential participants and/or their parents or guardians in a language that is understandable to them?"

DISCUSSION

Gene transfer research concepts are often difficult for potential participants to understand. Thus, particular care should be given to convey these concepts in the consent form in a readable and understandable manner. Readability and understandability are not synonymous; it is possible to make use of computerized readability scales and still have a consent form that is difficult to understand. Sometimes, reducing reading level without providing additional

TOOLS & BACKGROUND MATERIALS

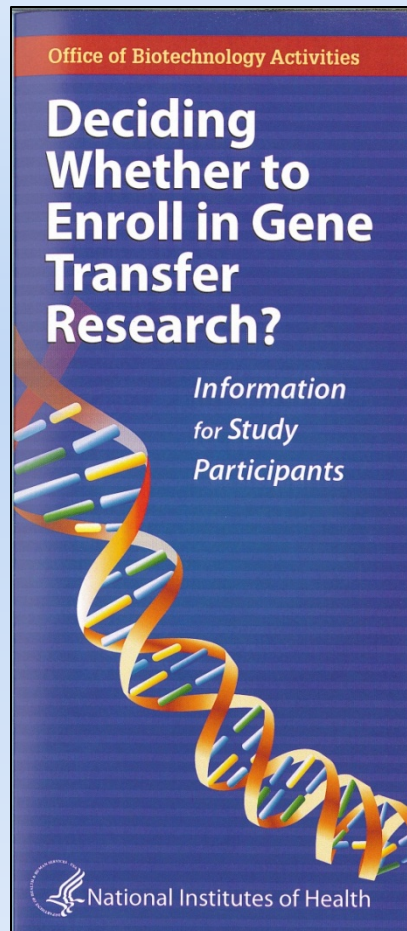
- ◆ [Simplification Guide to Medical Terms](#)
- ◆ [Dartmouth Informed Consent Evaluation Tool](#)
- ◆ [Written Assessment Tool](#)
- ◆ [Telephone Evaluation Plan](#)
- ◆ [FDA Guidance on Non-English Speaking Subjects](#)

MAIN POINTS

- ◆ Investigators should be attentive to using language easily read and understood by potential participants.
- ◆ Various methods and tools exist to improve and assess comprehension of information.
- ◆ All verbal and written



Other Resources



Helps potential participants understand fundamental concepts in human gene transfer research

Suggests questions participants should pose to their physicians and to research staff in order to make a fully informed decision about participation



GeMCRIS

- **Launched in 2004, GeMCRIS® is a Web-accessible database of human gene transfer clinical trials accessible by all.**
- **GeMCRIS is also a relational database that supports Web-based reporting of adverse event information directly to NIH.**
- **The development of GeMCRIS was a collaborative effort involving both the NIH and the FDA. Adverse event (AE) information captured in GeMCRIS also meets FDA reporting requirements.**



GeMCRIS

- **OBA and FDA can use GeMCRIS to analyze protocol and safety data**
 - **# of protocols using a vector**
 - **# of subjects dosed**
 - **Safety data can be searched across all 1200+ protocols based on event terms, MeDRA codes, relationship to gene transfer agent, vector, time interval between dosing and event**



GeMCRIS Analysis

- **In June 2011, OBA was notified of an unexpected death of a subject with leukemia on cancer vaccine trial**
- **Vaccine consisted of irradiated K562 cells transduced with a gene for human GM-CSF**
- **An unexpected finding in this case was the development of a profound eosinophilia with eosinophilia counts of $> 100,000/\text{ul}$ and high circulating levels of GM-CSF**



GeMCRIS Analysis

- **OBA notified 26 investigators with active protocols that either used K562 cells transduced with a gene for GM-CSF or irradiated tumor cells with GM-CSF**
- **OBA was able to notify the investigators that of the 71 protocols using these products, which together had dosed over 1700 subjects, only one other event with a mild, self-limiting eosinophilia was discovered**
- **Investigators invited to watch the webcast of the RAC meeting discussing this event and given the opportunity to participate**



Public Access to GeMCRIS

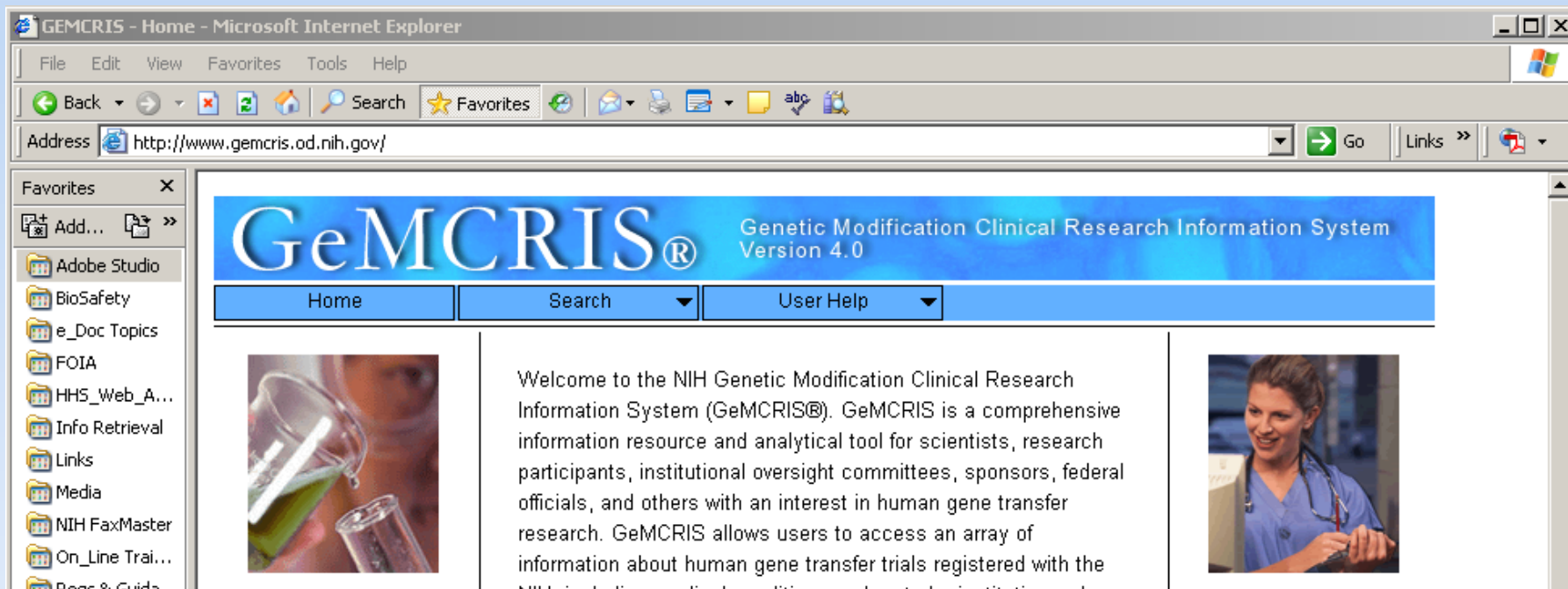
- **Promotes public access to information and understanding about human gene transfer clinical research**
- **Provides additional information that is not included in other data bases, such as Clinical Trials.gov**
 - Detailed information on product, including vector, promoters and specific transgenes
 - Scientific and non-scientific abstracts
 - Links to minutes if public review done
 - Summaries of major trial design changes



Public Access to GeMCRIS

- Type the following URL into your Web browser's address bar:

<http://www.gemcris.od.nih.gov/>





Finding Information

All clinical trial information is accessed through the “Search” functions on the Menu Bar

Search functions include:

- Protocol title and OBA Protocol numbers
- Medical condition (MedDRA coded)
- Trial Sites, study phase and trial status
- Product searches by:
 - Product name (includes synonyms e.g. “TK”)
 - Descriptors (controlled vocabulary)
 - Vectors, genetic elements, producer cells
 - Routes of administrations




Finding Information

Search Protocol Data

GeMCRIS®

Genetic Modification Clinical Research Information System
Version 6.2

[Home](#) [Search](#) [User Help](#)



Support

- Feedback
- Frequently Asked Questions
- Contact Us
- Browser Requirements

Search

Protocols	Search by Condition/Title
Principal Investigators	Search by Product
Vocabulary Reports	(GeMCRIS®). GeMCRIS is an information resource and analytical tool for scientists, institutional oversight committee members, regulatory officials, and others with an interest in human gene research. GeMCRIS allows users to access a wealth of information about human gene transfer trials registered with NIH, including medical conditions under study, trials being conducted, investigators carrying out the trials, gene products being used, route of gene product administration, and summaries of study protocols.

To facilitate access to this information, GeMCRIS provides preformatted reports. You can also create your own reports tailored to your particular information needs. To learn more about the "Search" menu item above, or click the "Frequently Asked Questions" link on the left to learn more about

GeMCRIS®

Genetic Modification Clinical Research Information System
Version 4.0

[Home](#) [Search](#) [User Help](#)

You may search the protocols by selecting any combination of the parameters below. If you wish to see all the protocols within GeMCRIS, leave the search fields empty and click the 'Search' button at the bottom of the page. Be aware that selecting multiple criteria will return only those protocols that match all of the constraints given.

If you would like to search for protocols by product description, then use this [Protocol Search by Product](#) link.

[Back](#)

Protocol Report Query Menu

Clinical Trial Title	<input type="text"/>
Medical Condition	<input type="text"/>
OBA Protocol Number	<input type="text"/> <input type="button" value="Search"/>
Clinical Trial Site	<input type="text"/>
Principal Investigator	<input type="text"/>
Study Phase	<input type="text"/>
Status	<input type="text"/>
<input type="button" value="Search"/> <input type="button" value="Reset"/>	

Search by Protocol Number, Medical Condition, or click 'Advanced Search' to do a detailed query. The search box below will find results based on the exact characters entered. Entering multiple words in the search box may limit your results.

Click a 'View' button to display information corresponding to that protocol or click 'View All' to display the information on all 29 protocols listed below.

View All

Search

Advanced Search or Protocol Search By Product

Quick" display

Gene Transfer Protocol Reports

Records 21 to 29 of 29

Previous 21-29

Protocol Number	Medical Conditions	Protocol Title	View Protocol
0703-839	Chemotherapy Cytomegalovirus test Glioblastoma multiforme Glioma Malignant glioma Neoplasm malignant	REGULATE: Regulatory T-Cell Inhibition with Daclizumab (Zenapax®) during Recovery from Therapeutic Temozolomide-induced Lymphopenia during Antitumor Immunotherapy Targeted Against Cytomegalovirus in Patients with Newly-Diagnosed Glioblastoma Multiforme	View
0710-878	Brain neoplasm Glioblastoma Glioma Medulloblastoma	A Pilot Feasibility Study of Oral 5-Fluorocytosine and Genetically-Modified Neural Stem Cells Expressing E. Coli Cytosine Deaminase for Treatment of Recurrent High-Grade Gliomas	View

Protocol Number: 1103-1095

Title: A Phase I/II Study of the Safety and Feasibility of Administering T Cells Expressing Anti-EGFRvIII Chimeric Antigen Receptor to Patients with Malignant Gliomas Expressing EGFRvIII

Phase: I (Phase Disclaimer)

Status: Active - 10/12/2012

Principal Investigator: Rosenberg, Steven A. National Cancer Institute - NIH

Medical Condition: Malignant glioma

Ex-vivo Cell:
Transducing Agent:
Genetic Element:

- » Primary autologous T lymphocytes
- » Envelope amphotropic Murine stem cell retrovirus gene transfer vector / PG13 packaging cell line
- » Murine stem cell virus (PCC4 embryonal carcinoma cell-passaged myeloproliferative sarcoma virus) long terminal repeat
- » Epidermal growth factor receptor scFv-CD28-CD3zeta-41BB CAR
- » 5' and 3' splice sites

Route of Administration:

Recommendation: Selected for Public Review

Public RAC Review Date: 06/08/2011

RAC Meeting Minutes: http://oba.od.nih.gov/oba/RAC/meetings/June2011/RAC_Minutes_06-11.pdf

Prot	Date	RAC Review Date	Type	Summary
Proc	09/30/2011	12/13/2011	M-L-C-1 Response	This submission is the 20 day letter notifying OBA that the trial has been initiated.
Abs				
Link				

HYPERLINKS:

- Investigator(s),
- Vector, cells, genes
- RAC minutes
- Abstracts
- Clinicaltrials.gov
- Amendments



Finding Information

Search Product Data

Protocol Report Query Menu

Product Name	<input type="text"/>
Vector Descriptor	<input type="text"/>
Vector Producer Cell Descriptor	<input type="text"/>
Genetic Element Descriptor	<input type="text"/>
Ex-vivo Cell Descriptor	<input type="text"/>
Nucleic Acid Descriptor	<input type="text"/>
Route of Administration	<input type="text"/>
<input type="button" value="Search"/> <input type="button" value="Reset"/>	

Product Name:

- Shorthand or other designations of constructs (e.g. GVAX, JX-594...)

Biological Descriptors:

- Vector Classes
- Producer Cells
- Genetic elements
- Transduced Cells

Routes of Administration

Multiple field entries return filtered data (“and” logic)

Vocabulary Reports

Term Reports

Search	Ex-Vivo Cell Vocabulary	
Protocols	Genetic Element Vocabulary	
Principal Investigators	Nucleic Acid Vocabulary	al Research
Vocabulary Reports	Vector Vocabulary	Term Report
information resource	VPC Vocabulary	Hierarchy Report

Ex-Vivo Cell Term Reports

Term Name	Definition	View Report
Allogeneic Umbilical Cord Blood-derived primary CD8+ and/or CD4+T cells.		View
Attenuated <i>Listeria monocytogenes</i> ANZ-100 (Δ actA/ Δ inlB)		View

Next 1-10

Vector Term Reports

Term Name	Definition	View Report
Adeno-associated virus 1 (AAV1) gene transfer vector	A human dependovirus [parvovirus] of serotype 1 that requires the presence of a helper virus (frequently Adenovirus) for productive infection. The linear single-stranded DNA genome of about 5000 nucleotides is packaged into an icosahedral particle	View

Records 1 to 10 of 174

Next 1-10

Nucleic Acid Term Reports

Term Name	Definition	View Report
_Study Design Terms	Category of terms related to various gene transfer study	View

Records 1 to 10 of 13

Next 1-10

Genetic Element Term Reports

Term Name	Definition	View Report
(C-C motif) ligand 21 [CCL-21] cDNA	(C-C motif) ligand 21 or CCL21 is one of several CC cytokine genes clustered on the p-arm of chromosome 9. The CC cytokines are proteins characterized by two adjacent cysteines. Similar to other chemokines the protein encoded by this gene inhibits hemopoiesis and stimulates chemotaxis. This protein is chemotactic in vitro for thymocytes and activated T cells, but not for B cells, macrophages, or neutrophils. The cytokine encoded by this gene may also play a role in mediating homing of lymphocytes to secondary lymphoid organs. It is a high affinity	View

Records 1 to 10 of 935

Next 1-10

User Help

GeMCRIS Overview

Welcome to GeMCRIS -- an electronic resource for healthcare administrators, the scientific community, and the general public.

With GeMCRIS, study investigators and people involved in the oversight of gene-transfer trials can record trial and *product* information -- as well as assess adverse events, or other clinical outcomes and events. This information may hold important implications for safety, and for future areas of *research*.

Gene transfer researchers can share information about ongoing gene-transfer trials, including:

- Names and contact information for fellow investigators
- Safety data
- Clinical outcomes and events associated with studies

Members of the public may also access GeMCRIS to find out what gene-transfer trials are being conducted, their trial locations, and principal investigator information. This information can assist in making decisions about participating in gene-transfer clinical trials.



Enhancements to GeMCRIS

- **Selected amendment summaries are now posted to the public-facing GeMCRIS pages**
- **In addition to adverse event reports, investigators can submit Annual Reports directly to GeMCRIS**



**Office of Biotechnology Activities
6705 Rockledge Drive, Suite 750
Bethesda MD 20892**

OBA@od.nih.gov

**For information on upcoming meetings join
our listserv.**



Gene Transfer Protocol Report



Protocol Number: 0401-624

Title: Phase I Trial of Conditionally Replication-Competent Adenovirus (Delta-24-RGD) for Recurrent Malignant Gliomas

Phase: I ([Phase Disclaimer](#))

Status: Active - 6/9/2011

Principal Investigator:

[Conrad, Charles A.](#), The University of Texas MD Anderson Cancer Center
[Lang, Frederick F.](#), The University of Texas MD Anderson Cancer Center

Medical Condition:

Brain neoplasm
 Glioblastoma multiforme
 Glioma

Product References:

Suzuki et al., 2001. A conditionally replicative adenovirus with enhanced infectivity shows improved oncolytic potency. Clin. Cancer Res. 7:120-126.

Dmitriev et al. 1998. An adenovirus with genetically modified fibers demonstrates expanded tropism via utilization of a coxsackievirus and adenovirus receptor-independent cell entry mechanism. J. Virol. 72 (12):9706-9713.

[deletion and modified](#)

[sequence](#)

Abstracts:

[Scientific Abstract Link](#)
[Non-Technical Abstract Link](#)

Link to ClinicalTrials.gov:

<http://www.clinicaltrials.gov/ct2/show/NCT00805376>

Amendments:

Date	RAC Review Date	Type	Summary
07/05/2012	09/11/2012	Annual Report	Annual report submitted. The study is open to enrollment.
04/19/2012	06/19/2012	Other	Amendment updates the language for reporting of adverse events to reflect the current policies and procedures for MD Anderson Cancer Center.
02/08/2012	06/19/2012	Other	Amendment updates the informed consent to include the latest information on side effects of dexamethasone.
09/02/2011	12/13/2011	Other	Amendment updates the informed consent document regarding providing access to patient information for purposes of study audits. For those subjects who are unable to consent (deceased, off-study or lost to follow-up) a waiver of consent is sought.
06/09/2011	09/13/2011	Annual Report	Annual report submitted. The study is open to enrollment.